Accuracy of contrast-enhanced ultrasound in the identification of thyroid nodules: a meta-analysis

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Abstract: This meta-analysis aimed to identify the accuracy of contrast-enhanced ultrasonography (CEUS) on the diagnosis of thyroid nodules. PubMed, Chinese Biomedical Medical databases (CNKI), Wan Fang (Chinese), and EBSCO database were searched from inception through April 15, 2015 without language and geographic restrictions. MetaDisc version 1.4 software was applied for this meta-analysis. We calculated the summary statistics for sensitivity (Sen), specificity (Spe), positive and negative likelihood ratio (LR+/LR-), diagnostic odds ratio (DOR), and receiver operating characteristic (SROC) curve. Twenty-five eligible studies were included in this meta-analysis. A total of 424 in 1154 nodules is malignant thyroid tumors. After all thyroid lesions were histologically confirmed by CEUS, the pooled Sen was 0.88 (95% confidence interval [CI] 0.85-0.91); the pooled Spe was 0.90 (95% CI 0.88-0.92). The pooled positive LR+ was 8.69(95% CI 5.78-13.09); the pooled negative LR- was 0.15 (95% CI 0.12-0.19). The pooled DOR of CEUS in the diagnosis of thyroid nodules was 63.18 (95% CI 37.82-105.53). The area under the SROC curve was 0.946 (standard error [SE] = 0.010). Our meta-analysis indicates that CEUS may have high accuracy in diagnosis of thyroid nodules. US is a traditional tool in the diagnosis thyroid nodules. However, with the development of science and technology, the emerging of CEUS significantly improve accuracy in the diagnosis thyroid nodules.

Keywords: Accuracy, ultrasound contrast imaging, CEUS, thyroid, nodules, meta-analysis

Introduction

Thyroid nodules are a common clinical problem. The prevalence of thyroid nodules is high in recent years, and approximately 8% of them may be an indicator of malignant nodules [1]. With the development of high-frequency ultrasound (US) imaging techniques, the detection rate of thyroid diseases has greatly been improved [2]. In spite of conventional US, as the preferred imaging method for diagnosing thyroid diseases, is inexpensive, worldwide available, non-invasive, no radiation and provides information regarding the characteristics associated with nature of thyroid nodules, such as margins, echogenicity, presence of microcalcification, and vascular flow. However, the US’s key limitation is weak in the differentiation benign from malignant nodules. In order to improve the accuracy in the diagnosis of thyroid nodules, a large number of methods for detection of thyroid nodules are assessed, such as Color-Doppler ultrasound (CDUS), Elastosonography, Contrast-enhanced ultrasound (CEUS) and so on. While CEUS has been used as an effective technique to improve the sonographic diagnosis of pseudocapsules in thyroid nodules, which is dynamic enhancement patterns of focal thyroid nodules immediately. CEUS has been introduced for diagnostic imaging in the renal, liver, heart, pancreas, trauma, and several other organs, which is based on employs microbubble contrast agents and complementary harmonic pulse sequences and ultrasound [3]. And CEUS can provide much better characterization of focal thyroid nodules than conventional US and the real-time of it has been widely applied to differentiate malignant from benign thyroid nodules in recent years. Some studies have proved the value in diagnosis of CEUS for thy-
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roid nodules [4-6]. However, few studies have analyzed the accuracy of CEUS in differentiating benign and malignant thyroid nodules. Therefore, present meta-analysis was objected to identify the accuracy of contrast-enhanced ultrasonography (CEUS) on the diagnosis of thyroid nodules.

Methods

Literature search

PubMed, Chinese Biomedical Medical databases (CNKI), Wan Fang (Chinese) and EBSCO databases were searched from inception through April 15, 2015 without language and geographic restrictions. The search terms include ultrasound, contrast-enhanced ultrasonography, ultrasound contrast imaging, CEUS, thyroid nodules, diagnostic accuracy. Meta-analysis or QUADAS. Literature review and manual search method were applied to prevent missing the literature. Two authors carried out the process of the literature retrieval. Any disagreement was resolved by a final consensus.

Selection criteria

The inclusion criteria for the current meta-analysis were as follows: (1) The clinical cohort study or diagnostic test was designed in the studies; (2) CEUS was used in differential diagnosis between malignant and benign thyroid nodules; (3) All thyroid nodules were diagnosed by CEUS firstly, then by pathologic diagnosis; and (4) Studies must conclude data for estimating sensitivity (Sen.), specificity (Spe), positive and negative likelihood ratio (LR+/LR-), and diagnostic odds ratio (DOR) with their 95% confidence intervals (CIs) was calculated. We obtained the summary receiver operating characteristic (SROC) curve and the corresponding area under the curve (AUC) [8]. The Spearman correlation coefficients were assessed to test the threshold effect. And we used the Cochran’s Q-statistic and I² test to judge potential heterogeneity between studies [9]. The I² statistic represented the percentage of total variation contributed by a between-study variation ranging from 0% to 100%. If I²>50% was indicated to be representative of statistically significant heterogeneity, then random effects model (the Mantel-Haenszel method) was used. If not, fixed-effects model (the Der-Simonian and Laird method) was applied [10]. For our original analysis, we limited meta-analysis to trials judged to be of low risk of bias.

Results

Study characteristics

Initially, one hundred and thirty potentially relevant articles were identified. After reviewing
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Table 1. Characteristic of case-control studies included in the study

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Language</th>
<th>Ethnicity</th>
<th>Sample size</th>
<th>Gender (M/F)</th>
<th>Age (years)</th>
<th>Instrument</th>
<th>Contrast-agent</th>
<th>2×2 table</th>
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<td>Asian</td>
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<td>48</td>
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<td>42</td>
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<td>SonoVue</td>
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<td>Chinese</td>
<td>Asian</td>
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<td>85</td>
<td>14/83</td>
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<td>33</td>
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<td>SonoVue</td>
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<td>72</td>
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<td>-</td>
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<td>10/36</td>
<td>52.1</td>
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</tr>
</tbody>
</table>
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practice chose the US to screen patients with suspected thyroid nodules firstly, because it's relatively inexpensive, worldwide available, non-invasive, lack of radiation and so on. But US is not a high degree of confidence in diagnosing or excluding malignancy thyroid nodules [23], With the development of science and technology, microbubble contrast agents were employed for US, then CEUS has emerged and gradually matured for diagnosing thyroid nodules [24]. Several early studies have implied that assessing nodules vascularity is essential in diagnosing nodules features [25]. Finding a valid modality to characterize the nodule lesion is necessary to differentiate malignant form benign nodules. Several recent studies indicated that CEUS is more accurate than other traditional inspections in detection and characterization nodules [4, 20]. But CEUS is less accurate than pathological diagnosis relatively.

In this meta-analysis pathological diagnosis is used as golden criterion that means absolutely exact accuracy. Therefore, CEUS just as an auxiliary diagnosis, before the pathological diagnosis is employed in differential diagnosis malignant form benign thyroid nodules. CEUS is still widely used in clinical practice but the accuracy of CEUS has controversy. So we made meta-analysis to systematically evaluate the accuracy of CEUS in the diagnosis of thyroid nodules was provided by our study. This Meta-analysis absorbed 12 independent studies.
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Figure 2. Forest plots for the accuracy of CEUS for the diagnosis of thyroid nodules (A. Sensitivity. B. Specificity. C. Positive likelihood ratio. D. Negative likelihood ratio).
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Figure 3. Forest plot of DOR of CEUS for the diagnosis of thyroid nodules.

Figure 4. SROC curve for the accuracy of CEUS in the diagnosis of thyroid nodules.

including 1003 thyroid nodules patients. The results showed that the pooled Sen, Spe, and DOR of CEUS in the diagnosis of thyroid nodules were 88, 90 and 63.18%, respectively. In summary, our results demonstrate that CEUS might have high accuracy for diagnosing thyroid nodules. So CEUS may be a good tool for differential diagnosis between benign and malignant thyroid nodules and plays an important role in predicting prognosis of thyroid nodules patients. Our results demonstrated that there was no significant correlation between Sen and Spe in the meta-analysis. Heterogeneity existed in early individual studies, but we were not carried out subgroup analyses. As a whole, our finding strongly suggests that CEUS is a high accuracy in qualitative diagnosis of thyroid nodules, which is consistent with early studies.

Limitations and strengths

There are some limitations in this meta-analysis. Firstly, our results indicated to be representative of statistically significant heterogeneity due to relatively low-quality included studies. Secondly, it exists some subjects’ selection bias in retrospective studies. In additions, the reliability and validity are adversely affected in our results due to the majority of included studies originated from China.

Conclusions

The meta-analysis implies that CEUS may have high accuracy in differential diagnosis between benign and malignant thyroid nodules. Therefore, CEUS may be a good tool for the diagnosis of thyroid nodules. However, further detailed studies are still required to confirm our finding due to the limitation mentioned above.

Acknowledgements

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Disclosure of conflict of interest

None.

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References


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